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14. ABSTRACT Medulloblastoma is the most common malignant pediatric brain tumor. Granule neuron precursors (GNPs) in developing cerebellum proliferate exponentially, and the misregulation of which has been linked to medulloblastoma formation. GNPs are unipotent and only give rise to granule neurons. However, using MADM, a mouse genetic mosaic model, we found that medulloblastoma contain glial cells that are trans-differentiated from transformed GNPs. Our preliminary data showed that specific ablation of tumor glia without harming tumor GNPs led to complete tumor remission, suggesting a tumor-supporting role for these trans-differentiated glia. Here we propose to analyze the tumor "social behavior" with two specific aims. First, we will investigate the tumor regressing process at the cellular level in vivo, and determine therapeutic parameters of glial ablation for medulloblastoma treatment. Second, we will investigate the molecular basis for glia-tumor crosstalk that sustains the tumor growth. In the past year, we have completed most of the work proposed in aim 1. Our data showed that the glial-ablation treatment not only results in complete remission free of relapses, but also remains quite effective for mice with late-stage tumors. These findings are particularly encouraging since they point to great potentials in targeting glial cells for treating medulloblastoma in human patients.					
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INTRODUCTION:

Medulloblastoma is the most common malignant pediatric brain tumor, resulting from the deviation from normal process of cerebellar development. Immediately after birth, granule neuron precursors (GNPs) on the surface of developing cerebellum proliferate exponentially. The misregulation of GNP proliferation has been linked to medulloblastoma formation. Fate mapping experiments demonstrated that GNPs are unipotent and only give rise to granule neurons. However, using MADM, a mouse genetic mosaic model with lineage tracing capability, we found that medulloblastoma contain glial cells that trans-differentiate from malignantly transformed GNPs. Our preliminary data showed that specific ablation of tumor glia without harming tumor GNPs led to complete tumor remission, suggesting a critical role for these trans-differentiated glia in supporting the growth of tumor GNPs. Here we propose to perform detailed mechanistic analyses for the tumor “social behavior” with two specific aims. First, we will investigate the tumor regressing process at the cellular level *in vivo*, and determine therapeutic parameters of glial ablation for medulloblastoma treatment. Second, we will investigate the molecular basis for glia-tumor crosstalk that sustains the tumor growth.

BODY:

To gain full mechanistic understandings of the “social behavior” in medulloblastoma, two aims of this grant were subdivided into thirteen tasks. Among all the tasks, we have completed **original tasks 1-6** in year 1 (July 2011 to June 2012), and reported progresses in June 2012. In the current fiscal year (July 2012 to June 2013), we made excellent progresses in the remaining tasks. Due to the move from University of Oregon to University of Virginia in January 2013, we revised the Statement of Work (see attached) to adjust the timeline of some tasks to compensate for the loss of time during the move. We also plan to perform an additional experiment (new tasks 3-6 in the revised SOW) with rationale detailed below. This report is written according to tasks in the revised SOW unless specified otherwise.

Task 0. We have successfully moved relevant lab personnel, equipment, and reagents to UVa. Now the lab is fully functional, we have started performing some cell culture and biochemistry experiments with materials collected before our move.

Task 1. We have submitted our animal protocol to UVa Animal Care and Use Committee, and got the approval. We have also submitted ACURO documents and IACUC approval by UVa to USAMRMC Office of Research Protections (ORP), and are waiting for the feedback from reviewers.

Tasks 2-6. All mouse work is on hold at this time, pending approval by ORP.

- Tasks 3-6 are **new**. Rationale: we decided to request a “DN-SNARE” mouse line to verify findings from completed original tasks 3-6 because of a small possibility that the GFAP-TK transgene could have leaky expression in tumor GNPs. The DN-SNARE transgene can block growth factor secretion from astrocytes when combined with GFAP-tTA transgene used in our lab. We believe that using this new line to verify our current findings is critical for minimizing potential artifacts.

Task 7. In year 1, we have successfully sub-fractionate tumor GNPs from medulloblastoma formed in our mouse model with a Purcoll-gradient based centrifugation method. Isolated tumor GNPs have high purity, free of glial cell contamination. In the current year while working at University of Oregon, we have also successfully purified and cultured astrocytes, and optimized

the culture conditions that can accommodate both GNPs and astrocytes, a prerequisite for co-culture experiment. We have performed two rounds of co-culture experiments. Based on the preliminary findings, we found that tumor GNPs adhere much better when co-cultured with astrocytes than to cultured alone [Fig 1A]. Additionally, tumor GNPs show higher proliferative rate when co-cultured with astrocytes in comparison to tumor GNPs that were cultured alone [Fig 1B]. Therefore, astrocytes appeared to support the adhesion and proliferation of tumor GNPs. We will continue on this task to generate statistically significant results after resuming our mouse work.

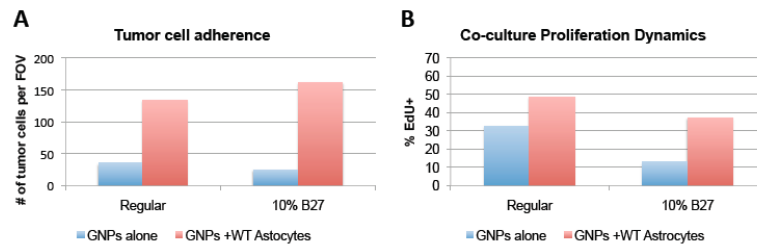


Figure 1. Astrocytes appear to support tumor GNPs in cell culture. A) Astrocytes support tumor GNP adhesion. B) Astrocytes support tumor GNP proliferation, especially in nutrition reduced culture condition.

Task 8. In year 1, we have successfully developed 1-color in situ hybridization technique on tumor sections, and resolved a few technical problems specifically related to tumor tissues (such as high background, degradation of tumor region at relatively high hybridizing temperature). To identify candidate growth factors before the completion of task 9 (RNAseq), we started performing qRT-PCR with whole tumor tissues to examine a panel of growth factors, and identified some candidate genes [Fig 2]. We will continue on this task after resuming our mouse work.

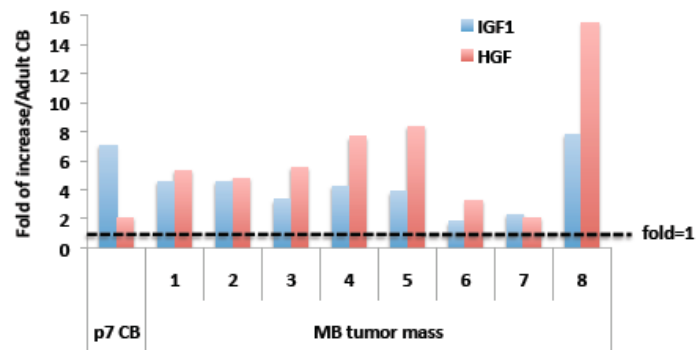


Figure 2. Elevated level of IGF1 and HGF in medulloblastoma. Compared to normal adult cerebellum (normalized as 1), both IGF1 and HGF are increased up to 15-fold in some tumors.

Task 9. we have performed one round of RNAseq analysis of tumor GNPs and are preparing to repeat the experiments and to analyze tumor astrocytes after optimizing the purification method.

KEY RESEARCH ACCOMPLISHMENTS:

- By completing original tasks 1-6, we observed significant therapeutic effects of astrocytic ablation, including a fast collapse of tumor mass, free of remission, and effective treatment for late stage tumors. The new experiment in revised tasks 3-6 will further solidify this important finding.
- We successfully mastered techniques to isolate tumor GNPs and WT astrocytes to high purity, and observed potential tumor-supporting activity of astrocytes in the preliminary co-culture experiments.
- We have performed substantial amount of analysis for tumor supporting factors with both candidate gene and global search methods.

- We have successfully moved our lab to University of Virginia. The medical community and highly collaborative basic research units at UVa should greatly facilitate our research progresses in the remaining year of this grant.

REPORTABLE OUTCOMES:

- **Invited speaker.** Ventura, P.B., Karfilis, K., Wahl, K., **Zong, H.** Medulloblastoma Builds Its Own Glial Niche. *Cold Spring Harbor Laboratories Meeting, "Glia in Health and Disease"*, July 19-23, 2012
- **Invited speaker.** Applications of MADM, a mouse genetic mosaic model, to basic and translational research. *School of Medicine Research Retreat, University of Virginia*, February 9-10, 2013
- **Invited speaker.** Genetic mosaic mouse models for brain tumors: basic research and pre-clinical applications. *Neuro tumor club dinner meeting, Society of Neuro-oncology*, Washington DC, April 8, 2013
- **Invited speaker.** Studying lineage potential in tumorigenesis using MADM, a genetic mosaic system. *AACR Annual Meeting*, Washington DC, April 6-10, 2013
- **Invited speaker.** Understanding tumor cell maneuvers in brain tumors with MADM, a genetic mosaic system. *Brain tumor meeting*, Berlin, Germany, May 23-24, 2013

CONCLUSIONS:

In the past two years, we have completed the work proposed in aim 1, demonstrating that the ablation of tumor astrocytes could have dramatic therapeutic effect on tumor GNPs. However, we did notice that the GFAP-TK transgene used by us could have minor leakage into tumor GNPs. Therefore, we are in the process of requesting two additional transgenic lines to confirm our findings in aim 1. In the current year, our lab moved from University of Oregon to University of Virginia to gain access to world-renowned experts in signal transduction and the medical community. With the support of UVa leadership and the dedication of lab members, the lab has started full operation within two months of moving and has started generating data for the project. The most exciting progress in year 2 is the breakthrough in cellular fractionation and co-culture experiment to investigate the supporting role of tumor astrocytes. Our preliminary data have demonstrated that tumor GNPs adhere better and proliferate more actively in the presence of astrocytes, compared to when cultured alone. We also performed qRT-PCR based screening of growth factors in the tumor mass, and identified two candidate genes IGF1 and HGF. In the coming year, we will further examine the source of these growth factors and their role in tumor GNP growth. In summary, our studies could identify niche factors that are critical for medulloblastoma development, and lead to the development of novel therapeutic strategies.

APPENDICES:

- Abstract for *Cold Spring Harbor Laboratories Meeting, "Glia in Health and Disease"*, July 19-23, 2012
- Abstract for *Neuro tumor club dinner meeting, Society of Neuro-oncology*, Washington DC, April 8, 2013
- Abstract for *AACR Annual Meeting*, Washington DC, April 6-10, 2013
- Invitation and meeting flier of Brain Tumor Meeting in Berlin, Germany

MEDULLOBLASTOMA BUILDS ITS OWN GLIAL NICHE

Brit Ventura, Kate Karfilis, Kelsey Wahl, Hui Zong
Institute of Molecular Biology, University of Oregon

Understanding the interactions between tumor cells and their microenvironment/niche are paramount for the design of novel and effective treatments. However, conventional research methods, including mouse cancer models, lack the in vivo single-cell resolution to tease apart tumor versus niche cell types for mechanistic insights. To circumvent this problem, our lab makes use of a novel mouse genetic system termed MADM (Mosaic Analysis with Double Markers) to model cancers. Starting with a mouse heterozygous for a tumor suppressor gene (TSG), MADM can generate sporadic mutant cells that are null for candidate TSG(s) with unequivocal labeling of GFP, enabling us to trace the lineage of mutant cells and distinguish them from neighboring normal cells.

In this study, we used MADM to model medulloblastoma, the most prevalent type of pediatric brain tumors. It is known that such tumors, especially the desmoplastic subtype relying on Shh pathway hyperactivation, originate from granule neuron precursors (GNPs). It is puzzling that although GNPs are unipotent toward the granule neuron lineage, the tumor mass often contains glial cells. Moreover, medulloblastomas are often highly vascularized even though GNPs are known not to produce angiogenic factors. Using the GNP-specific Math1-Cre, the MADM model generated GFP+ *p53*-null GNPs in a heterozygous *patched* mutation background, which resulted in fully penetrant cerebellar tumors. Although the majority of green cells in the tumor mass resemble GNPs, a closer look revealed a population of green cells with large cell bodies, reminiscent of astroglial morphologies. We further confirmed their glial identity by staining with multiple astrocyte markers. Importantly, the fact that these cells are GFP+ suggests that they are derived from mutant GNPs. It's surprising since normal GNPs are known not to give rise to any glial cells. To investigate the molecular mechanisms that enable mutant GNPs to generate glia within the tumor, we performed transcriptome analysis of tumor GNPs in comparison to wildtype GNPs and discovered the increased expression of transcription factors that are normally restricted to a small time window during embryonic GNP lineage development. It suggests that tumorigenic transformation might lead to a reversion of the fate of some tumor GNPs to an earlier developmental stage with broader potentials. In addition to investigating the mechanisms of trans-differentiation, we are also analyzing the functional roles of tumor glial cells, in particular their roles in inducing angiogenesis to support tumor GNPs.

In summary, our MADM-based medulloblastoma model seems to have revealed a community building behavior of tumor cells, through which some of them convert their fate to non-proliferative glial cells, which in turn provide cues for the establishment and maintenance of the tumor microenvironment.

18th Annual Neuro-Tumor Club Dinner Meeting at AACR

Time: Monday April 8, 2013; 6:30–10:00pm

Location: Washington Plaza Hotel, 10 Thomas Circle, NW, Washington, DC 20005

* **Yes, I would like to present at the Neuro-Tumor Club Dinner Meeting!**

(Abstract deadline Friday, March 8, 2013)

☐ **Yes, I plan to attend the Neuro-Tumor Club Dinner Meeting!**

(RSVP required even if you are not presenting)

Name: _____ Hui Zong_____

Institution: _____University of Virginia, Dept of Microbiology, Immunology, and Cancer Biology_____

Title (student / postdoc / professor, etc): _____Associate Professor_____

Phone: _____434-982-1956_____ Email: _____hz9s@virginia.edu_____

Presentation Title: _____Genetic mosaic mouse models for brain tumors: basic research and pre-clinical applications_____

I would like to present* in one the following areas:

- ☐ Geno/Phenotyping and Personalized/Combinatorial Therapy
- ☐ Angiogenesis and Tumor Microenvironment
- ☐ New Gene and Immunotherapy
- ☐ New Tools and Translational Approaches
- ☐ CNS Metastases
- ☐ Biomarkers in Gliomas?
- ☐ Stem Cells
- * ☐ Animal Models
- ☐ Other category? _____

* Presentation is **5-minutes**, no more than 5 slides (without animation), PowerPoint file to be e-mailed to SNO by Monday, April 1.

Key Message of Presentation (< or = 3 sentences): (instead of formal abstract)

We developed a genetic mosaic model called MADM that can generate sparse, GFP-labeled mutant cells in the mouse brain, mimicking the clonal origin of human tumor physiology [Zong 2005 Cell, Muzumdar 2007 PNAS].

Single-cell resolution provided by the model allows one to study brain tumor at pre-transforming stages for cell of origin issues [Liu et al 2011 Cell], and to study tumor-niche interactions without ambiguity.

As a pre-clinical model, MADM allows one to 1) quantify drug efficacy by cell number rather than tumor size; 2) analyze drug effects on mutant/tumor cells outside of tumor mass; 3) monitor tumor cell migration; 4) assess tumor-prevention effects of a given drug on pre-transforming cells.

I would be interested to deliver a 3-minute INTRODUCTION on the following theme:

- ☐ Geno/Phenotyping and Personalized/Combinatorial Therapy
- ☐ Angiogenesis and Tumor Microenvironment
- ☐ New Gene and Immunotherapy
- ☐ New Tools and Translational Approaches
- ☐ CNS Metastases
- ☐ Biomarkers in Gliomas?
- ☐ Stem Cells
- ☐ Animal Models
- ☐ Other category? _____

Presenter Application Form Due: Friday, March 8, 2013

Please **email** this form to Linda Greer: linda@soc-neuro-onc.org or **FAX** to: 713-583-1345

Human cancers frequently arise from the loss of both copies of a tumor suppressor gene (TSG) in sporadic cells. We have established a mouse genetic system termed MADM (Mosaic Analysis with Double Markers) that limits TSG inactivation in very few cells for physiologically relevant cancer modeling. MADM unequivocally labels sporadic mutant and wildtype sibling cells with GFP and RFP respectively, to confer the *in vivo* single cell resolution and lineage tracing capability. The research theme of our lab is focused on brain tumor modeling with two questions that are particularly interesting to us: 1) What is the developmental origin of brain tumors? 2) How do tumor cells evolve along their lineage potentials during malignant transformation?

The cell-of-origin for glioma has long been thought to be neural stem cells (NSCs) based on two observations. First, purified tumor cells manifest stem cell features. Second, the introduction of p53 and NF1 mutations into NSCs in mouse models led to glioma formation. However, endpoint features may not reliably reflect the nature of tumor initiating cells, thus the analysis should focus on early, pre-transforming stages. Furthermore, conceptually there is a critical difference between cell-of-origin and cell-of-mutation. The former is the cell type that transforms into malignancy, while the latter is the one in which initial mutations occur but may not directly transform. We used MADM to probe into early phases of gliomagenesis, and surprisingly found the lack of overpopulation of mutant NSCs. Among NSC-derived cell types, we only detected dramatic over-expansion of mutant oligodendrocyte precursor cells (OPCs) at pre-transforming stages. Consistently, terminal-stage tumor cells displayed salient OPC features by both histological criteria and transcriptome profiling. Most importantly, introducing the same mutations directly into OPCs was sufficient for malignant transformation. Our findings strongly implicate OPC as a cell-of-origin for glioma, and highlight the importance of analyzing early phases of tumorigenesis to pinpoint its origin.

Our lab also generated a medulloblastoma model by introducing TSG mutations into uni-potent granule neuron precursors (GNPs). Preliminary findings indicated that tumor GNPs divert from their uni-potency to give rise to glial cells. We are currently investigating two critical questions on these tumor-derived glial cells: 1) how do uni-potent GNPs reprogram themselves during malignant transformation to generate cell types beyond the original lineage potential? 2) how do glial cells contribute to the progression of medulloblastoma?

In summary, our work has started unraveling the importance of lineage potentials during the tumorigenic process. While the same mutations could occur in many cell types, often times only one cell lineage would be able to transform into malignancy. Teasing apart the differences in signaling context between transforming and non-responsive cell types could provide critical insights for devising highly effective treatment strategies. It's also important to note that tumor cells have the capacity to deviate from normal developmental program and alter their original lineage potentials. The mechanisms and significance of "tumor-reprogramming" still await further investigations.

MDC → Zelluläre Neurowissenschaften → Robert-Rössle-Str. 10 → 13092 Berlin-Buch

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Berlin, 21.08.12

Brain Tumor Meeting 2013, Berlin

Dear Dr. Zong:

Berlin has a very large neuroscience community, and one major focus is on brain tumors. Several Berlin-based research groups have specialized on investigating the impact of parenchymal interactions of brain tumor cells. A focus is given on the interaction of brain tumor cells with immune cells (microglia) and neural stem- and precursor-cells.

For the Departments of Neurosurgery at the Charité and the Clinics in Berlin-Buch the properties and the treatment of brain tumors are a major topic. There are close and stimulating collaborations between several groups doing basic research and the clinics. This led to the idea to organize a small conference on brain tumors and to complement the local expertise with external experts. We started the first meeting in 2000 and will have the sixth meeting of this series in 2013. Last time over 170 participants attended the meeting. The meeting will take place at the Max Delbrück Center for Molecular Medicine (MDC) in Berlin-Buch. It will start on Thursday, May 23, 2013, after lunch and will end in the afternoon of the next day on Friday, May 24, 2013.

We would like to invite you to join this meeting and to give a lecture on the role of tumor stroma interactions in cancer. We feel that it would be very stimulating for brain tumor-researchers to get an overview on the many important pathological roles that have been uncovered for tumor-parenchyma interactions in peripheral tumors.

We can cover your travel costs (economy flight) and accommodation. We are convinced that this will be an exciting meeting and we would be very happy if you could accept our invitation.

Looking forward to hearing from you,

Sincerely,



Helmut Kettenmann

Contact

Meino Alexandra Gibson
Max Delbrück Center for Molecular Medicine
Robert-Rössle-Straße 10, D-13125 Berlin
gibson@mdc-berlin.de
Telefon: +49 30 94 06-33 36
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Registration fee

Participants (early)	Euro 30,--
Students (early)	Euro 10,--
Participants (late)	Euro 50,--
Students (late)	Euro 30,--

Registration

Important Deadlines
March 1, 2013: Abstract submission
March 1, 2013: Early registration
Until April 15, 2013: Late registration

For registration and abstract submission
please visit:
<http://www.braintumor-berlin.de>
Onsite registration will be available.

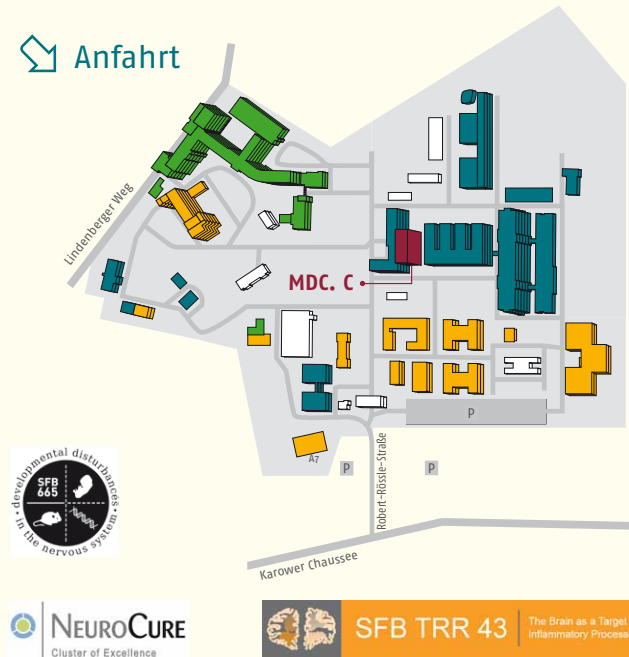
Public transportation

S-Bahnhof Berlin-Buch (S2)
Bus 158

Final program available April 2013.



 Anfahrt



Organized by

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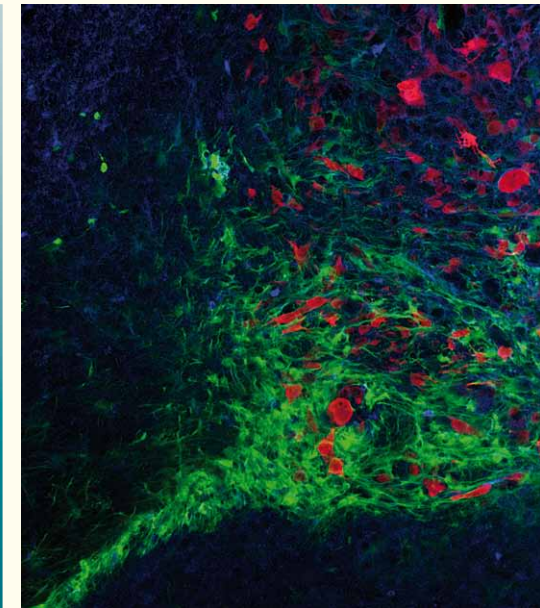
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Max Delbrück Center for Molecular
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Charité-Universitätsmedizin Berlin
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Brain Tumor 2013

Announcement

May 23-24, 2013
Campus Berlin-Buch
Max Delbrück Communications Center
(MDC.C)
Robert-Rössle-Str. 10 • D-13125 Berlin

Dear Colleagues,

We are pleased to announce that the Brain Tumor Meeting 2013 will take place at the Max Delbrück Center für Molecular Medicine (MDC) in Berlin (Germany) on May 23-24, 2013.

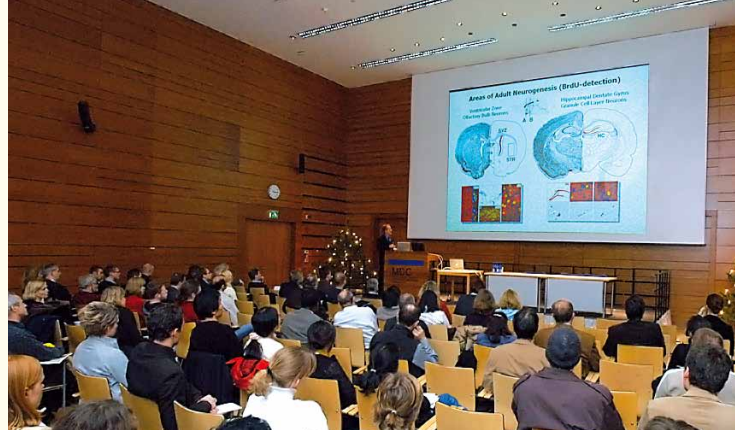
In summer 2000, Berlin neuroscientists, neurosurgeons and neurologists focusing on brain tumors initiated this scientific conference. It was repeated in 2001, 2004, 2006, 2008 and 2011 - throughout this time the Brain Tumor Meeting gained national and international attention and attracted many leading scientist working on gliomas and other brain tumors.

The main focus of the meeting is to provide a platform for an interdisciplinary scientific exchange especially between scientists and clinicians. Recent discoveries on the role of glioma stem cells, on the interaction of gliomas with their microenvironment and on glioma cell death pathways have altered our understanding of glioma biology.

Internationally and nationally renowned speakers were invited to present their newest data on these topics. Furthermore, abstracts for oral- and poster-presentations are invited and the best resentations will be awarded prizes.

We expect exciting scientific exchange and invite you to join this meeting.

Scientific Program Committee



Invited Speaker

Gabriele Bergers (San Francisco, USA)

Ruggero De Maria (Rome, Italy)

Bozena Kaminska (Warsaw, Poland)

Michael Platten (Heidelberg, Germany)

Jeremy N. Rich (Cleveland, USA)

Peter Vajkoczy (Berlin, Germany)

Michael Weller (Zurich, Switzerland)

Hui Zong (Oregon, USA)

Scientific Program Committee

Rainer Glass, Frank Heppner, Helmut Kettenmann, Jürgen Kiwit, Michael Synowitz

Abstracts

Abstract submissions for oral or poster presentation are welcome.

Deadline for abstract submission is March 1, 2013.

Duration of oral presentation:

talk: 15 min

discussion: 5 min

The official meeting language is English.

Best Abstract Prize Competition

Prizes are awarded for the best five abstracts presented at the Brain Tumor 2013 meeting.

- | | |
|----------|----------------|
| 1. prize | iPad |
| 2. prize | iPad mini |
| 3. prize | iPod touch 64G |
| 4. prize | iPod touch 32G |
| 5. prize | iPod nano |

A two-tier assessment will be used to determine Best Abstracts Prize: First by the members of the program committee and second by a voting system of the meeting participants.